

Pharmacokinetic Report



CEDRA DCN 11-657-T1

Mylan Pharmaceuticals Inc. PRIL-0367

Pharmacokinetic Report

**Quality Assurance Audits and Inspections**

Phase	Date of Audit or Inspection	Date Reported to CEDRA Project Director	Date Reported to CEDRA Management
Data	November 21, 2003	November 21, 2003	November 21, 2003
Report	December 4, 2003	December 4, 2003	December 5, 2003

This study was audited and inspected by CEDRA's Quality Assurance Unit and the findings reported on the dates listed above.

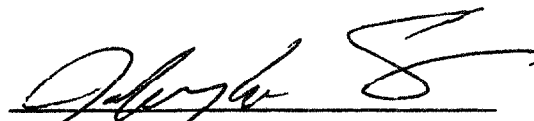
Michel Malone for Robert Orozco 12/5/03

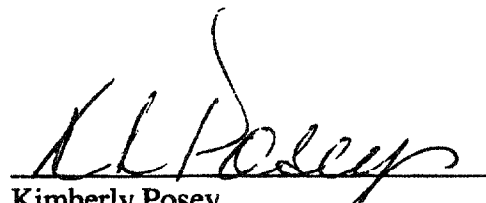
Robert Orozco
Quality Assurance Unit
CEDRA Corporation



Guidance for Industry Compliance Statement

These analyses were conducted and reported in compliance with applicable Guidance on Bioavailability and Bioequivalence Studies For Orally Administered Drug Products-General Considerations and Guidance on Statistical Approaches to Establish Bioequivalence prepared by Division of Bioequivalence, Office of Generic Drugs, Food and Drug Administration, and per CEDRA SOPs.

 12/5/03
Jeffrey G. Stark, Ph.D.
Senior Scientist, Pharmacokinetics
CEDRA Corporation

 12-5-03
Kimberly Posey
Quality Control
CEDRA Corporation

Introduction

Omeprazole is indicated for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD). It is indicated for the short-term treatment of diagnostically confirmed erosive esophagitis (associated with GERD). Omeprazole, in combination with clarithromycin and amoxicillin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. [Excerpt from Protocol PRIL-0367]

This study was designed to compare the rate and extent of absorption of two products of omeprazole, 20 mg PRILOSEC OTC tablets (Procter & Gamble) and 20 mg PRILOSEC capsules (manufactured for AstraZeneca LP by Merck & Co. Inc.), following a single oral dose (1 x 20 mg) in healthy volunteers under fasting conditions.

Study Design

This was a randomized, single-dose, two-way crossover study designed to compare the rate and extent of absorption of two products of omeprazole, 20 mg PRILOSEC OTC tablets (Procter & Gamble) and 20 mg PRILOSEC capsules (manufactured for AstraZeneca LP by Merck & Co. Inc.), under fasting conditions. Drug administrations were separated by a minimum of 7 days.

Clinical Procedures Summary

In this two-period crossover study designed to compare the rate and extent of absorption of two drug products, healthy adult volunteers randomly received the two separate drug administrations in assigned periods, one per period. Dates for Period I were October 18 – 19, 2003 and dates for Period II were October 25 – 26, 2003. Forty-eight subjects participated in the

study and no alternates were enrolled. Three subjects did not complete the study. See the Clinical Summary for additional information about the study conduct.

Procedures for Collecting Samples for Pharmacokinetic Analysis

Blood samples were drawn prior to dosing (pre-dose) and at 0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 14, and 16 hours post-dose. All samples were collected at the scheduled timepoints unless noted otherwise in the Clinical Summary. Samples were frozen at approximately -70 °C pending shipment to CEDRA Corporation for analysis.

Bioanalytical Summary

Plasma samples were analyzed using the CEDRA Corporation validated LC-MS-MS procedure, ATM-601. Bioanalytical results were collected and processed by Analyst (Version 1.3.1, Applied Biosystems/MDS SCIEX, Foster City, CA/Concord, Ontario) before importation into Watson LIMS (Version 6.4.0.02, InnaPhase Corporation, Philadelphia, PA). See the Method Validation Report and Bioanalytical Report sections for details of the method validation and sample analysis procedure.

Pharmacokinetic and Statistical Analyses

The concentration-time data stored in the Watson LIMS System were transferred directly to WinNonlin (Enterprise Version 4.0, Pharsight, Cary, NC) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin using WinNonlin Model 200 for extravascular input.

Concentration-time data that were BLQ (< 1.00 ng/mL) were excluded from calculations prior to data summarization and pharmacokinetic analysis. Data were summarized by scheduled (nominal) sampling times. Actual elapsed times were used for all pharmacokinetic and statistical

analyses. All sample time deviations reported by PRACS Institute, Ltd. were included in the calculations, see Clinical Summary.

Pharmacokinetic Methods

The following pharmacokinetic parameters were calculated for each subject and treatment.

C_{\max}	The maximum drug concentration in plasma determined directly from individual concentration-time data
T_{\max}	Time to reach maximum concentration
C_{last}	The last quantifiable drug concentration determined directly from individual concentration-time data
T_{last}	Time of the last measurable concentration
λ_z	The observed elimination rate constant estimated using linear regression of the log concentration versus time profile for each subject. The points used for calculating λ_z were selected after visual inspection of the data. At least three data points clearly in the elimination phase were necessary to determine λ_z .
$T_{1/2}$	The observed terminal elimination half-life calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
AUC_{last}	The area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as: $AUC_{\text{inf}} = AUC_{\text{last}} + \frac{C_{\text{last}}}{\lambda_z}$
$AUC_{\text{Extrap}} (\%)$	The percentage of AUC_{inf} based on extrapolation

Statistical Procedures

The non-transformed and natural logarithmic transformed pharmacokinetic parameters were analyzed for differences between treatments using an ANOVA model with factors for sequence, subject within sequence, period, and treatment (1).

$$Y_{ijk} = \mu + S_{ik} + P_{jk} + F_j + e_{ijk}$$

where

Y_{ijk}	=	Pharmacokinetic response, e.g. C_{max} or $\ln(C_{max})$
i	=	Number of subjects
k	=	Number of sequences
j	=	Number of formulations
μ	=	The overall mean
S_{ik}	=	The random effect of the i th subject in the k th sequence
F_j	=	Fixed effect for the j th formulation
P_{jk}	=	Fixed period effect at the j th formulation in the k th sequence is administered
e_{ijk}	=	The random error in observing Y_{ijk}

The 90% confidence intervals for the ratios (Test Product: Reference Product) of the least squares means of the non-transformed parameters C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z , and $T_{1/2}$, were calculated. The Wilcoxon Signed Rank Test was used for a nonparametric comparison of T_{max} values and a significant difference was defined *a priori* as $p < 0.05$.

The natural logarithmic transformation of the pharmacokinetic exposure parameters of omeprazole, $\ln(AUC_{last})$, $\ln(AUC_{inf})$, and $\ln(C_{max})$, were used to assess bioequivalency as recommended in FDA guidance for statistical approaches to establishing bioequivalence (2) and

the FDA guidance for bioavailability and bioequivalence studies of orally administered drug products (3). The 90% confidence interval for the ratio of the geometric means of the Test Product and the Reference Product was calculated for each parameter. Bioequivalence is established if the 90% confidence intervals for $\ln(\text{AUC}_{\text{last}})$, $\ln(\text{AUC}_{\text{inf}})$, and $\ln(\text{C}_{\text{max}})$ are within the 80% - 125% interval (4).

Validation Statement

Statistical analysis was performed in WinNonlin (Enterprise Version 4.0) using the Linear Mixed Effects Module. The Wilcoxon Signed Rank Test was performed in SAS (Version 8.2, SAS Institute Inc.). WinNonlin and SAS were validated according to CEDRA SOPs prior to being utilized for pharmacokinetic and statistical data analyses.

Results and Discussion

Of the initial participants, Subjects 6, 17, and 46 did not complete the study and samples from these subjects were not assayed upon the request of the sponsor. Pharmacokinetic data from forty-five subjects were imported into WinNonlin and included in the analyses. Watson concentration-time data with descriptive statistics are shown in Tables P1 and P2. Data are presented graphically in Figures P1 through P48; Figure P1 contains plots of mean data on linear and semi-logarithmic scales, Figures P2 and P3 contain plots for all subjects by treatment, and Figures P4 through P48 contain concentration-time profiles for individual subjects.

As shown in Tables P1 and P2, the first quantifiable concentrations were observed at the 0.25-hour sample time for each product. The highest mean plasma concentrations (mean \pm SD) of omeprazole, 207 ± 269 ng/mL for PRILOSEC OTC tablets and 178 ± 238 ng/mL for PRILOSEC capsules, occurred at 1.33 hours and 3.00 hours after administration, respectively. At the end of the pharmacokinetic sampling period, omeprazole concentrations were below the limit of quantification for most subjects. At the 16-hour sample time, quantifiable data were

observed for 3 subjects after the administration of PRILOSEC OTC tablets and 4 subjects after the administration of PRILOSEC capsules.

The results of the pharmacokinetic analysis are contained in Tables P3 through P7. Tables P3 and P4 contain the pharmacokinetic parameters with descriptive statistics for Treatments A and B, respectively. Tables P5 through P7 contain comparisons of log-transformed and non-transformed exposure parameters and estimates of individual bioequivalence based on AUC_{last} , AUC_{inf} , and C_{max} . The pharmacokinetic parameters for omeprazole are summarized in the following table.

Parameter	<u>Treatment A:</u> PRILOSEC OTC Tablets				<u>Treatment B:</u> PRILOSEC Capsules			
	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	45	2.50	1.19	47.62	45	2.73	1.19	43.35
C_{max} (ng/mL)	45	431	303	70.45	45	351	296	84.14
AUC_{last} (hr*ng/mL)	45	772.9	907.8	117.47	45	767.9	991.1	129.07
AUC_{inf} (hr*ng/mL)	45	778.3	920.9	118.33	45	777.8	1017	130.73
AUC_{Extrap} (%)	45	0.44	0.43	97.96	45	0.82	1.33	162.67
λ_z (hr ⁻¹)	45	0.9265	0.2971	32.07	45	0.8107	0.2977	36.73
$T_{1/2}$ (hr)	45	0.85	0.37	43.23	45	1.19	1.51	127.17
T_{last} (hr)	45	8.44	2.90	34.37	45	9.29	2.81	30.21
C_{last} (ng/mL)	45	2.71	5.58	206.17	45	3.74	9.57	255.65

The results of the statistical analyses are contained in Tables P8 through P10. Table P8 contains the results of the ANOVA for the non-transformed pharmacokinetic parameters, Table P9 contains the results of the ANOVA for log-transformed exposure parameters, and Table P10 contains the results of the Wilcoxon Test for comparing T_{max} values in different treatments.

As shown in Table P8 for the non-transformed parameters, the confidence intervals were within the 80% - 120% range of AUC_{last} , AUC_{inf} , and T_{max} , but not for C_{max} , λ_z , and $T_{1/2}$. The p-value from the Wilcoxon test (Table P10) was 0.1365, $p > 0.05$, indicating that the difference

in observed T_{max} values in the omeprazole formulations was not significant. The results of the ANOVA for log-transformed values of C_{max} , AUC_{last} , and AUC_{inf} are summarized in the table below. Detailed information is contained in Table P9.

Dependent Variable	Geometric Mean		Ratio (% Test/Ref)	90% Confidence Interval	
	Test	Ref		Lower	Upper
$\ln(C_{max})$	355.5146	272.5349	130.45	116.91	145.55
$\ln(AUC_{last})$	550.3056	524.1326	104.99	100.65	109.52
$\ln(AUC_{inf})$	552.7085	528.4631	104.59	100.31	109.05

The 90% confidence intervals were within the 80% - 125% interval for the transformed systemic exposure parameters $\ln(AUC_{last})$ and $\ln(AUC_{inf})$. However, the upper limit for the 90% confidence interval for $\ln(C_{max})$ was not in the accepted range.

Pharmacokinetic Data Archiving

The data, report, and electronic media will be archived off-site for a minimum of fifteen years according to applicable CEDRA Standard Operating Procedures.

Contributors

Jeffrey G. Stark, Ph.D.	Senior Scientist, Pharmacokinetics
Shilpi Khan, M.S.	Biostatistician
Rosa Carrasco	Pharmacokinetic Project Associate
Alma Martinez	Quality Control
Kimberly Posey	
Robert Orozco	Quality Assurance Unit

Conclusions

- The 90% confidence intervals for comparing total systemic exposure, $\ln(\text{AUC}_{\text{last}})$ and $\ln(\text{AUC}_{\text{inf}})$, of PRILOSEC OTC tablets to PRILOSEC capsules are within the 80% - 125% interval.
- The 90% confidence interval for comparing the maximum exposure, $\ln(C_{\text{max}})$, of PRILOSEC OTC tablets to PRILOSEC capsules were 117% -146%, which is outside of the accepted 80% - 125% interval required for bioequivalence. It is worth noting that the point estimate (130%) was outside this interval as well, indicating that it is highly unlikely that bioequivalence could be demonstrated in a larger study.
- Therefore, PRILOSEC OTC tablets distributed by Procter & Gamble and PRILOSEC capsules manufactured for AstraZeneca LP by Merck & Co. Inc. are not bioequivalent.

References

1. Shein-Chung Chow and Jen-Pei Liu Chapter 6: Transformed Analysis of Individual Subject Ratios "Design and Analysis of Bioavailability and Bioequivalence Studies" (2nd edition), Published by Marcel Dekker, 2000; p161.
2. "Guidance For Industry: Statistical Approach to Establishing Bioequivalence" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) January 2001.
3. "Guidance For Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) October 2000.
4. Shein-Chung Chow and Jen-Pei Liu Chapter 4: Statistical Method For Average Bioavailability "Design and Analysis of Bioavailability and Bioequivalence Studies" (2nd edition), Published by Marcel Dekker, 2000; p98.